

The Dichotomy Between Benzene and Fulvene Formation in Palladium-Catalyzed Domino Tricyclizations of 2-Bromotetradec-1-ene-7,13-diynes

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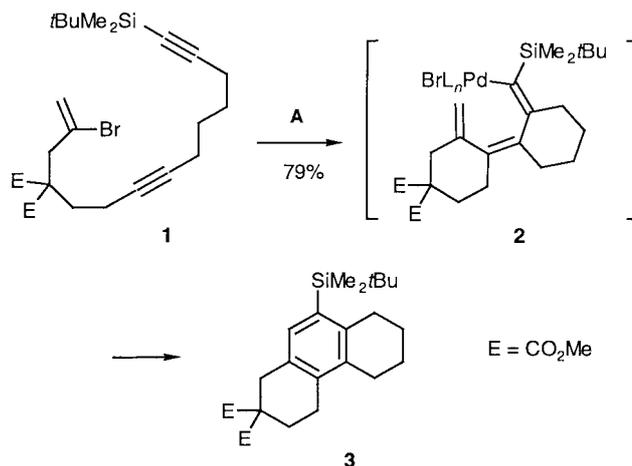
Received 7 December 2001

Abstract: 2-Bromotetradec-1-ene-7,13-diynes **1**, **5**, **12** with different substituents at the acetylenic terminus under palladium catalysis have been found to either yield an angularly bisannulated benzene derivative **3** (79%), or fulvene derivatives of type **5** (52–74%) as well as monoannulated fulvenes **13b–e** (32–48%). The mechanisms for all three reaction modes most probably involve intramolecular 5-*exo-trig* carbopalladations of an intermediate 1,3,5-hexatrienyl-6-palladium bromide intermediate.

Key words: palladium catalysis, cross coupling, cascade cyclizations, fulvenes

Transition-metal-catalyzed C-C-bond forming reactions have been widely explored in the past 15 years. Among them, palladium-catalyzed cross-couplings have attracted considerable attention in both academic and industrial research laboratories.¹ Towards the construction of complex organic molecules from relatively simple open chain precursors, the Heck reaction is particularly attractive, as it is compatible with a variety of functional groups and can be incorporated more than once in multistep sequential processes² following a number of distinctly different reaction pathways.^{1,3} Thus, single operation tricyclizations of 2-bromoalk-1-enediynes have been used to prepare carbocyclic as well as heterocyclic angularly bisannulated benzene derivatives in moderate to good yields.⁴ All previously reported examples, however, contained either two five- or one five- and one six-membered ring attached to the aromatic central ring. In order to test the accessibility of the octahydrophenanthrene skeleton by this route, we have prepared several 2-bromotetradec-1-ene-7,13-diynes and subjected them to typical Heck cross-coupling conditions.⁵

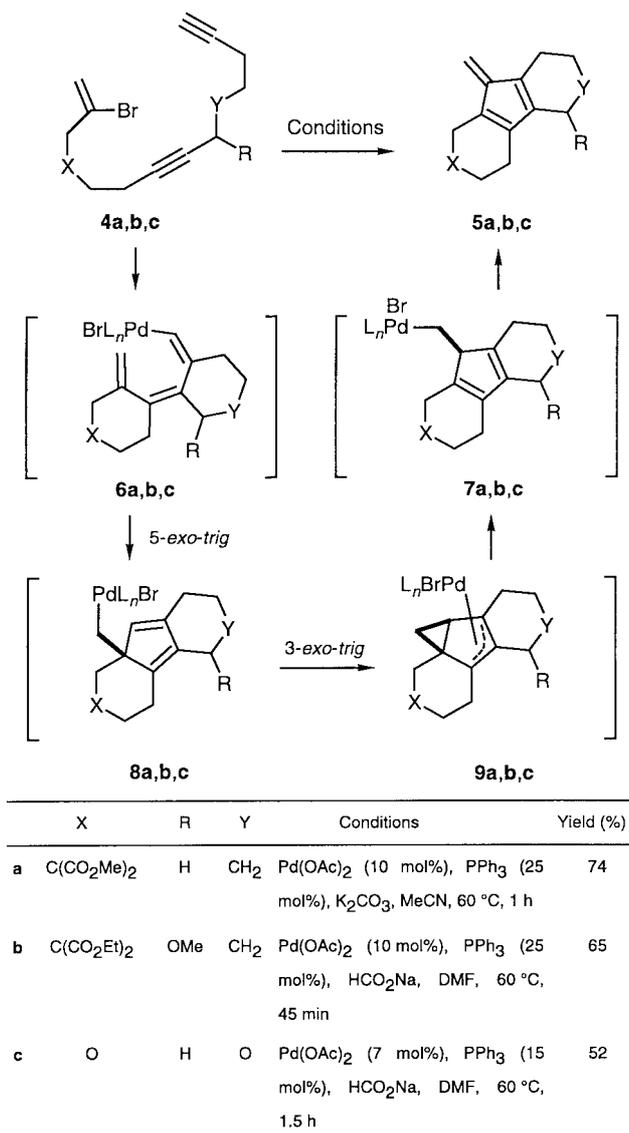
Upon treatment of dimethyl 2-bromo-14-(*tert*-butyldimethylsilyl)-tetradec-1-ene-7,13-diyne-4,4-dicarboxylate (**1**) with palladium acetate in the presence of triphenylphosphine and potassium carbonate in acetonitrile at 60 °C for 20 h, it was smoothly converted into dimethyl (9-*tert*-butyldimethylsilyl)-1,2,3,4,5,6,7,8-octahydrophenanthrene-2,2-dicarboxylate (**3**).⁶ This transformation appears to have proceeded via a 6-*endo-trig* cyclization or a 6 π -electrocyclization of the alkenylpalladium intermediate **2**, (Scheme 1), followed by α,β -dehydropalladation.



Scheme 1 A: Pd(OAc)₂ (10 mol%), PPh₃ (25 mol%), K₂CO₃ (3 equiv.), MeCN, 60 °C, 20 h.

In contrast, dimethyl 2-bromotetradec-1-ene-7,13-diyne-4,4-dicarboxylate (**4a**) which was obtained from **1** by hydrodesilylation at the acetylenic terminus, under identical conditions did not yield the unsilylated octahydrophenanthrene, but the bisannulated fulvene derivative **5a** within 1 h in 74% yield (Scheme 2).⁷ The 9-methoxy-substituted analog **4b** and the heteroanalogous bromoenediyne **4c**, under slightly modified conditions, reacted in the same way to give the fulvenes **5b** in 65% yield within 45 min, and **5c** in 52% yield within 1.5 h, respectively. The structure of the fulvene **5b** was rigorously proved by an X-ray crystal structure analysis of the Diels-Alder adduct that was readily formed upon treatment of **5b** with dimethyl acetylenedicarboxylate (Figure).⁸

The formation of fulvenes **5** may be rationalized in terms of a 5-*exo-trig*-carbopalladation instead of the 6-*endo-trig*-cyclization discussed above, at the stage of the intermediate **6** to give a neopentyl-type intermediate **8**, which subsequently undergoes a 3-*exo-trig* carbopalladation. The resulting cyclopropylmethylpalladium intermediate equilibrates with the cyclopropane-annulated π -allylpalladium complex **9**. A subsequent cyclopropylcarbonyl to homoallyl rearrangement would lead to the σ -homoallylpalladium complex **7** which by β -dehydropalladation would yield the fulvene **5** (Scheme 2).



Scheme 2

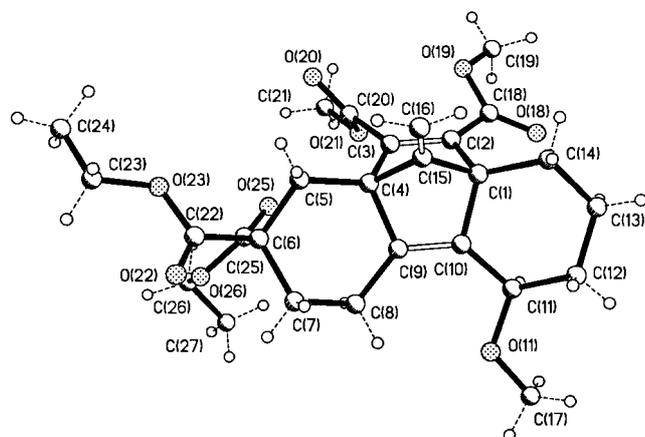
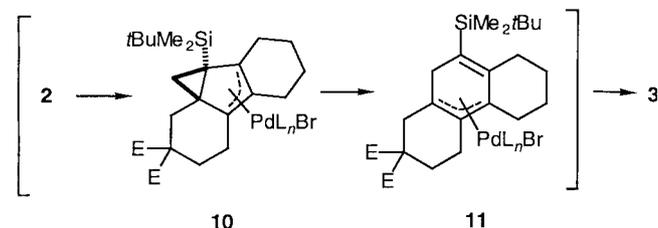


Figure Structure of the Diels-Alder adduct of dimethyl acetylenedicarboxylate to the fulvene **5b** in the crystal.⁸

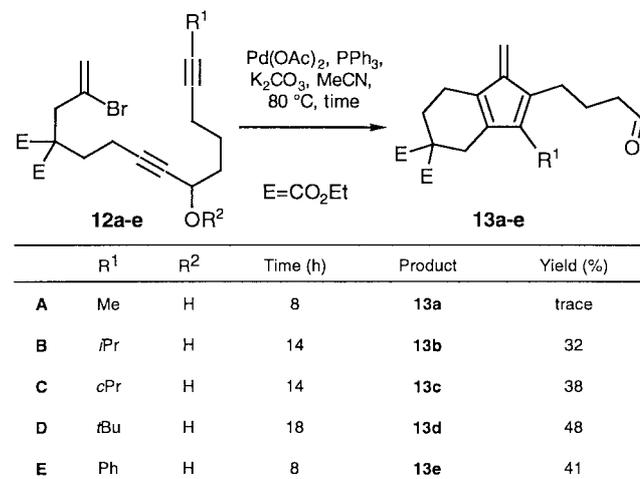
Considering this reaction mode it comes to mind that the formation of the octahydrophenanthrene **3** might actually also occur via a 5-*exo-trig* and subsequent 3-*exo-trig* carbopalladation to give a cyclopropane-bridged intermediate of type **9** which in that case would be the trialkylsilyl-substituted species **10**. Induced by the trialkylsilyl substituent, another mode of ring opening might be favored in **10** leading to **11**, and β -dehydropalladation would then lead to **3** (Scheme 3).



Scheme 3

In order to determine the apparently crucial effect of the trialkylsilyl substituent in **1** on the reaction mode, a number of 2-bromotetradec-1-ene-7,13-diynes **12a-e** with different substituents on the acetylenic terminus were prepared.⁵ Several attempts to tricyclize the phenyl- and cyclopropyl-substituted enediynes **12e** ($R^2 = \text{Me}$) and **12c** ($R^2 = \text{Me}$) failed completely. Neither could a bisannulated benzene nor a corresponding fulvene derivative be isolated. Although the reasons for this failure are not obvious, the examples show that steric factors apparently do not promote the cyclization mode that would lead to the octahydrophenanthrene skeleton.

Surprisingly, however, the same enediynes **12a-e** ($R^2 = \text{H}$) with a propargylic hydroxy instead of a methoxy group upon treatment with the palladium catalyst, did cyclize to yield fulvenes **13a-e**, yet of a distinctly different substitution pattern compared to the fulvenes **5** described above (Scheme 4). The 9-substituted diethyl 7-methylene-8-(4'-



Scheme 4

oxobutyl)bicyclo[4.3.0]nona-1(6),8-diene-3,3-dicarboxylates **13a-e** undoubtedly must also arise by some sort of tricyclization with subsequent opening of the C ring.

The fact that the exocyclic methylene group, the carbon atom of which must have originated from the bromovinyl group of the precursor **12**, in the product **13** resides four carbon atoms away from the malonate moiety, can only be rationalized assuming a complex rearrangement involving an alkyl shift within the molecule.

The possible mechanism involving a two-fold sequence of 3-*exo-trig*-cyclization, σ - π - σ and consecutive cyclopropylmethyl- to homoallylpalladium rearrangement and a final [2+2] cycloreversion is currently under investigation.

In conclusion, the reported palladium-catalyzed cascade cyclizations enhance the scope of accessible skeletons and offer a feasible way to some potentially interesting highly substituted fulvenes.

Acknowledgement

This work was supported by the Fonds der Chemischen Industrie. We are indebted to BASF AG, Bayer AG and Degussa-Hüls AG for generous gifts of chemicals. We also thank Dr. Burkhard Knieriem for his careful proofreading.

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- Intra-intermolecular sequences leading to monoannulated benzene derivatives have been reported by several groups; cf. (a) Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777–778. (b) Negishi, E.-i.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253–3256. (c) Torii, S.; Okumoto, H.; Nishimura, A. *Tetrahedron Lett.* **1991**, *32*, 4167–4168. (d) Parsons, P. J.; Stefinovic, M.; Willis, P.; Meyer, F. E. *Synlett* **1992**, 864–866. (e) Negishi, E.-i.; Ay, M.; Sugihara, T. *Tetrahedron* **1993**, *49*, 5471–5482.
- The cyclization precursors **1**, **4a-c** and **12a-e** were easily assembled in six to ten steps according to routine procedures applying malonate alkylations, alkylolithium additions to aldehydes, and alkylations on appropriate building blocks with alkyl bromides as C–C-bond forming steps.
- All new compounds were fully characterized by IR, NMR (^1H , ^{13}C) and mass spectra as well as correct elemental analyses or high-resolution mass spectral data.
- Pentasubstituted fulvenes have been obtained under Heck conditions from vinyl bromides and disubstituted alkynes; cf. Silverberg, L. J.; Wu, G.; Rheingold, A. L.; Heck, R. F. *J. Organomet. Chem.* **1991**, *409*, 411–420.
- Crystallographic data (excluding structure factors) for the structure of the Diels-Alder adduct of **5b** with dimethyl acetylenedicarboxylate have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-160097. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Article Identifier:

1437-2096,E;2001,0,SI,0920,0922,ftx,en;Y21100ST.pdf